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·Review·

Can multi-modal neuroimaging evidence from hippocampus provide biomarkers for the progression of amnestic mild cognitive impairment?

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Impaired structure and function of the hippocampus is a valuable predictor of progression from amnestic mild cognitive impairment (aMCI) to Alzheimer's disease (AD). As a part of the medial temporal lobe memory system, the hippocampus is one of the brain regions affected earliest by AD neuropathology, and shows progressive degeneration as aMCI progresses to AD. Currently, no validated biomarkers can precisely predict the conversion from aMCI to AD. Therefore, there is a great need of sensitive tools for the early detection of AD progression. In this review, we summarize the specific structural and functional changes in the hippocampus from recent aMCI studies using neurophysiological and neuroimaging data. We suggest that a combination of advanced multi-modal neuroimaging measures in discovering biomarkers will provide more precise and sensitive measures of hippocampal changes than using only one of them. These will potentially affect early diagnosis and disease-modifying treatments. We propose a new sequential and progressive framework in which the impairment spreads from the integrity of fibers to volume and then to function in hippocampal subregions. Meanwhile, this is likely to be accompanied by progressive impairment of behavioral and neuropsychological performance in the progression of aMCI to AD.

Keywords: Alzheimer's disease; amnestic mild cognitive impairment; hippocampus; episodic memory; functional magnetic resonance imaging; structural magnetic resonance imaging; diffusion tensor imaging; multi-modal MRI biomarker

Introduction

Mild cognitive impairment (MCI) is considered to be an intermediate cognitive state between normal aging and dementia[1]. Based on the profile of cognitive impairment, MCI can be further classified into several subtypes including amnestic MCI (aMCI) or non-amnestic MCI and single-domain MCI or multi-domain MCI. Single-domain aMCI involves only a deficit in memory, whereas in multi-domain aMCI the impairments involve memory and at least one other cognitive domain. Accordingly, single-domain non-amnestic MCI is diagnosed if the impairment involves a single non-memory domain, whereas the multi-domain form refers to deficits in multiple non-memory domains[1, 2]. The aMCI subtypes are considered to be the most likely to progress to AD[2]. Thus, early and comprehensive detection of the transitional stages of disease progression is of great importance for intervention and delay of the clinical symptoms of dementia.

In general, episodic memory deficit is typical in AD and involves the abilities to retain, recall, and encode information related to personal events and experiences occurring at specific times and places[3, 4]. The hippocampus plays a pivotal role in processing episodic memory[5] and is one of the earliest regions affected by AD neuropathology[6]. Structural and functional changes in the hippocampus are

valuable indicators of possible progression from aMCI to AD. Neuroimaging techniques for evaluating hippocampal function are useful in the assessment of disease progression and trajectory and the related pathology[7]. Previous studies have indicated that hippocampal atrophy is the most prominent structural hallmark of progression from aMCI to AD[8, 9]. Therefore, it is reasonable to assume that structural and functional changes in the hippocampus are important in understanding the origins of impaired memory function in AD.

A biomarker is a parameter that can be considered as an indicator of normal biological processes, pathogenic processes, or pharmacological reactions to therapeutic drugs[10]. While most people with aMCI progress to AD, others develop non-AD (i.e. Parkinson's disease, vascular dementia, *etc.*), remain in the aMCI state, or revert to normal. Any increase in the ability to predict the outcome of aMCI will be invaluable for counseling patients, advising on disease-modifying treatments, and programming clinical trials[11]. Accordingly, there is a strong need for specific and sensitive tools or biomarkers as aMCI progresses to AD, with an emphasis on early diagnosis and disease-modifying treatments. To date, however, no available biomarkers can distinguish aMCI converters from non-converters.

In recent years, most attention on aMCI has been focused on two main research questions—how to predict the progression of aMCI to AD, and which measures protect against conversion to dementia in disease-modifying clinical trials. In this review, we provide a brief summary of recent hippocampal research in aMCI patients, with special emphasis on the combination of multi-modal MRI biomarkers based on neurophysiological, neuroimaging, and neuroanatomical data.

Multi-Modal Neuroimaging Techniques in the Hippocampus of aMCI Patients

aMCI, the assumed pre-stage of AD, has been extensively described with regard to the underlying pathology of AD. Therefore, most current studies have probed for potential surrogate markers of disease progression. Multi-modal neuroimaging techniques are powerful tools for creative exploration of the epidemiology, diagnostic sensitivity, progression, and therapeutic targets for aMCI. Numerous candidate measures have also been used in cross-sectional and longitudinal neuroimaging studies. Recently, advanced analytical techniques have become available, further improving our ability to discover disease-associated pathological changes and clinical correlations *in vivo*.

Structural MRI in the Hippocampus of aMCI Patients

Structural magnetic resonance imaging (sMRI)-based image analysis has the potential to automatically track brain atrophy at multiple time-points. sMRI has demonstrated that fine-scale anatomical changes are associated with cognitive decline and occur in a spreading pattern that mirrors the advance of pathology[12]. Therefore, the extent of brain degeneration in aMCI can be quantified using structural techniques such as MRI alone.

Using different image analysis techniques in cross-sectional studies, researchers have revealed marked structural changes in the hippocampus of aMCI patients. Mostly, the hippocampal gray matter (GM) volume in aMCI patients is smaller than controls, but larger than in AD, and has a left-right asymmetric pattern of atrophy[13-16], although inconsistent findings have also been reported[17]. Recently, Fouquet and colleagues have also demonstrated that memory-encoding deficits appear to be specifically linked to atrophy of the hippocampal CA1 subfield, while the episodic retrieval impairment seems to be caused by a more distributed tissue loss in aMCI[18]. Using semi-automatic segmentation of hippocampal subfields, Pluta and colleagues have demonstrated that the volumes in aMCI are reduced in CA1 and the dentate gyrus (DG), as well as the head and tail subfields of the hippocampus compared to controls, and significant differences are found in the bilateral hippocampal volumes[19]. Notably, based on the above studies, variability of atrophy has been found between the left and right hippocampus and in different subregions of the hippocampus in different aMCI studies. Nonetheless, the complementary findings highlight the fact that the deficits in aMCI seem to be in a left-right asymmetric pattern and are associated with different hippocampal subregions. This raises the possibility of a distinct sequential progression of atrophy of hippocampal subregions in aMCI patients. Furthermore, the variation suggests that the hippocampus needs to be divided into more precise subregions based on structure and function.

In longitudinal studies, the importance of subicular and CA1 volume as a biomarker for aMCI conversion has been studied using different techniques in different numbers of patients. Most of the studies found that smaller hippocampal volumes, predominantly in the subicular and CA1 areas, are related to an increased risk for conversion from aMCI to AD[20-24], despite some inconsistent findings[25, 26]. Furthermore, hippocampal volumes are associated with the presence of one or two APOE ε4 alleles in aMCI, which can accelerate the accumulation of subsequent clinical pathology of AD[27-29]. Interestingly, Arlt and colleagues have shown that loss of GM in the left hippocampus is correlated with poorer performance on the Boston Naming Test, Mini-Mental Status Examination, and trail-making test B in aMCI over time[30]. Notably, although these studies used different analysis techniques and follow-up times (1, 2, 3, or 6 years), they consistently indicate that the hippocampal atrophy is greater in aMCI converters than non-converters, and further suggest that hippocampal subregions, especially CA1 and the subiculum, can better predict the conversion of aMCI to AD. Therefore, more attention should be paid to the interaction between hippocampal volume and APOE genotype, which may contribute to the varied results.

In addition, to precisely distinguish aMCI from controls, aMCI converters from non-converters, and aMCI from AD, several highly accurate quantitative studies have been performed. For example, Pennanen and colleagues have reported that the overall classification by total hippocampal volume between AD patients and controls is 90.7% (sensitivity, 85.4%; specificity, 94.9%), and that between AD and aMCI patients is 80.5% (sensitivity, 77.1%; specificity, 83.1%)[31]. Jack and colleagues have also reported that the odds ratio for progression to sporadic AD over 1.2–4.8 years is 1.75 in aMCI patients with smaller hippocampal volumes when compared to those with larger hippocampal volumes[32]. In a 3-year donepezil/vitamin E/placebo study of aMCI, Jack and colleagues further demonstrated a higher hippocampal atrophy rate (5.44%) in the placebo group than in the others[23]. Using hippocampal atrophy data from different time points (0, 6, 12, 18, 24, and 36 months), Leung and colleagues demonstrated that the rates in aMCI patients accelerated by 0.22%/ year^2, and the acceleration of hippocampal loss may contribute to the progression of aMCI to AD[33]. However, all of the studies were based on data-driven methods, which do not generate a precise cut-off value that separates MCI converters from non-converters. In addition, most of these studies based their MCI diagnosis on clinical grounds alone, without usng a neuropsychological score as a cut-off. Further, these studies were based on a relatively small sample size, which may influence the statistical power. This can also explain some of the discrepancies and may lead to overestimation of the classification rate.

Diffusion Tensor MRI in Hippocampus of aMCI Patients

Diffusion tensor imaging (DTI) is a noninvasive and quantitative MRI technique that can assess the orientation and integrity of white matter (WM) tracts by measuring the diffusion of water molecules in the living human brain[34]. Most studies use DTI measures of mean diffusivity (MD) and fractional anisotropy (FA) as markers of cerebral integrity, although the decomposition of individual eigenvalues to axial and radial diffusivity is becoming more common. MD provides a measure of translational diffusion, and FA provides a measure of the directionality of diffusion. In intact tissues, MD is restrained by barriers to free diffusion and FA is determined by the parallel organization of the tissue[35].

The number of studies using the DTI approach to examine WM integrity in aMCI has greatly increased over time. Furthermore, DTI has been considered to be sensitive in exploring hippocampal changes[36]. For example, Fellgiebel and colleagues have demonstrated that aMCI patients show increased MD and decreased FA in the left hippocampus, with no significant changes in the right hippocampus[37]. However, Mulle and colleagues evaluated the cross-sectional discriminative accuracy of hippocampal volume and DTI measures with regard to aMCI and demonstrated increased MD and reduced FA in the bilateral hippocampus, particularly on the left side[38]. This could be used as a sensitive cross-sectional marker for detecting subtle hippocampal abnormalities related to aMCI[38]. Using the tract-based technique, Zhou and colleagues examined pathways connecting the hippocampal region to the posterior cingulum and the hippocampal region to the whole brain in a sample of aMCI patients and healthy controls. They demonstrated a significant reduction in the

number of fibers in the pathways from the hippocampus to the whole brain only in the aMCI patients[39], which indicates that the neurobiological changes associated with aMCI may be detectable, especially at the neuronal and axonal levels.

In a recent cross-sectional study, Cherubini and colleagues used the DTI method to detect microstructural changes in aMCI and observed damage (MD increase) in the bilateral hippocampus relative to controls, but no differences in FA values[40]. Lee and colleagues have demonstrated that aMCI patients show reduced FA in the fornix, which is associated with decreased anterior CA1 and antero-medial subiculum thickness[40]. Furthermore, both reduced fornix FA and hippocampal volume are linked to reduced episodic memory, but only hippocampal volume predicts episodic memory in models including both hippocampal and fornix predictors[41]. Converging findings suggest that aMCI patients present with microstructural damage in the hippocampus (increased MD, reduced FA, or both), which may be explained by increased intercellular space and elevated extracellular water content as well as by degenerative neuronal loss and Wallerian degeneration. However, it remains unknown whether the detectable DTI changes in WM are due to amyloid or neurofibrillary tangle formation, microvascular disease, or other as yet unknown processes.

In addition, the DTI technique has recently been used to discover relationships between brain-wide WM integrity and cognitive ability in old age[42]. A higher MD of the hippocampus is associated with worse memory performance, while FA of the hippocampus is not associated with memory performance[43]. However, none of these studies assessed the relationship between microstructural damage in the hippocampus and memory performance in aMCI. Numerous studies have also demonstrated that the hippocampal subfields are differentially affected by pathological damage, and DTI parameters may be more sensitive and quantifiable measures of early degeneration in AD than conventional MR imaging techniques[44]. Another important consideration is that a few studies using DTI measures report no differences in FA values of the hippocampus in aMCI patients. This indicates that changes in anisotropy in the whole hippocampus as an ROI may not be easily detected by DTI during aMCI, as atrophy occurs in different subregions from shape analysis[45], and may only be apparent at a later stage of disease progression. Furthermore, most studies were performed with small sample sizes, so statistical power was decreased, and they differed in disease characteristics (e.g. level of cognitive impairment), both of which may lead to increased variability. Also, the diagnostic criteria for aMCI are not uniform and longitudinal follow-up is generally lacking. The use of ROIs instead of whole-brain voxelwise or tract-based approaches may provide differential sensitivities for group differences in DTI measures. Finally, differences in scanning parameters such as voxel size, may introduce differences into partial volumes, causing measurement differences between studies.

Functional MRI in the Hippocampus of aMCI Patients

Functional magnetic resonance imaging (fMRI) is a noninvasive technique that does not require the injection of a contrast agent. This method reflects synaptic activity through changes in blood flow and the oxyhemoglobin: deoxyhemoglobin ratio[46]. fMRI also measures the interregional temporal correlations between spontaneous blood oxygenation level-dependent (BOLD) fluctuations and neurophysiological activity in spatially separated, but functionally related brain regions at rest or during task performance[47]. The fMRI approaches mainly include resting-state fMRI (R-fMRI) and task-based fMRI. R-fMRI experiments are relatively free of subject compliance and training demands[47], making this approach especially attractive to dementia researchers. In task-activation fMRI, the neuronal response depends on the type of task, the severity of cognitive impairment, and the participant's attention and motivation[48]. It is difficult to study the functional connections between spatially isolated brain regions that are activated by task-specific fMRI approaches.

There is increasing evidence that alterations in synaptic function occur very early in the disease process of AD, possibly long before the progression of clinical symptoms and even significant neuropathology[49]. It follows that fMRI may be a particularly useful technique for detecting changes in brain function that are present very early in the progression of AD. In this section, we review fMRI data regarding functional abnormalities of the hippocampus in aMCI.

Resting-State Functional MRI

Recently, R-fMRI has attracted increasing attention and

has also been extensively used on the hippocampus of aMCI patients. Numerous R-fMRI cross-sectional studies have demonstrated altered hippocampal connectivity with cortical and subcortical regions in aMCI patients, who can be characterized by abnormalities in resting-state hippocampal connectivity. Recently, in our research group, Li and colleagues have demonstrated that the regional coherence of R-fMRI signals within the hippocampus decreases significantly in aMCI patients. These data can be used to differentiate between aMCI patients and controls[50]. Bai and colleagues selected the whole hippocampus as the ROI and found that aMCI patients show significantly lower hippocampal functional connectivity (FC) with the prefrontal, temporal, and parietal lobes, and the cerebellum[51]. Bai and colleagues further divided the bilateral hippocampus into six subregions as seeds and have indicated that decreased FC of these subregions is related to episodic memory declines in aMCI patients. The sensitivity is 83.3% and the specificity 91.7% when differentiating aMCI patients from controls, and the sensitivity is 83.3% and the specificity 83.3% when differentiating progressing from stable aMCI patients[52]. In a recent fMRI study, Xie and colleagues selected the whole hippocampus as the ROI and have also shown diminished hippocampal FC with the right frontal, left temporal, and insular regions. These findings may be associated with the impairment of episodic memory and cognitive decline in the early stage of AD[53]. Based on these studies, the complementary findings consistently emphasize that the impairment of episodic memory in aMCI patients may be directly associated with decreased FC of some of the hippocampal subregions within the temporal cortex.

Furthermore, our research group has been advancing the FC study of the hippocampus in aMCI patients by improving different methodologies. Our studies have routinely divided the hippocampus into more precise subregions, established the association of FC with neuropsychological performance, and increased the statistical power by using large samples[52, 53]. A longitudinal aMCI study from another research group has also indicated that the left hippocampus has significantly reduced connectivity with the right parahippocampal gyrus and bilateral hippocampus. The right hippocampus shows significantly decreased connectivity with the left cuneus, right parahippocampal gyrus, right posterior cingulate cortex (PCC), and left hippocampus after 3 years in aMCI patients[53]. Moreover, long-delayed memory scores are significantly positively correlated with connectivity within the left hippocampus itself. In addition, MMSE scores are positively correlated with the connectivity between the left inferior temporal gyrus and the right hippocampus[54].

In contrast, Qi and colleagues have used the FC analysis method and found that impairment and compensation coexist in the disease progression of aMCI[55]. Accordingly, other recent studies have also shown both increased and decreased hippocampal connectivity in aMCI patients. For example, Bai and colleagues have shown that the hippocampus has increased connectivity with more diffuse areas of the brain in aMCI patients. Those regions associated with increased FC with the hippocampus have a significantly negative correlation with episodic memory performance[51]. Wang and colleagues have found that baseline increases are followed by longitudinal decreases in the left and right hippocampal FC in aMCI patients, suggesting that the initially reported enhanced connections are a compensatory process[54]. Moreover, Das and colleagues have also reported increased FC between the entorhinal cortex (ERC) and the anterior hippocampus in aMCI patients[56]. Xie and colleagues have shown increased FC with the left PCC, the left caudate, and the right occipital gyrus. This suggests that aMCI patients can recruit network resources, primarily from the frontoparietal regions, to compensate for the losses due to the degenerative process of the disease. The increased connectivity between the hippocampus and PCC offsets the disruption of the hippocampal–temporal connectivity in early aMCI[53]. Numerous studies have demonstrated and proposed that decreased input from the ERC to CA3/DG due to reduced integrity of the perforant pathway, which is particularly vulnerable to early AD pathology, is related to the hyperactivity reported in CA3 neurons in aging rodents and humans[57, 58]. Furthermore, this hyperactivity may relate to increased connectivity with outputs to the ERC. Therefore, the increased FC may have allowed more input from those regions into the hippocampus. Converging evidence suggests that patients with aMCI can use different brain areas and employ unique strategies for storing and recalling information, presumably as a compensatory mechanism for cognitive decline[59]. Furthermore, this increased connectivity attempts to bolster

stabilization of the resting-state network as neuropathology spreads in aMCI and may represent an attempted compensatory response to AD neuropathology.

The above studies, however, did not explore full-scale information from the whole brain, manually draw ROIs, use small and nearby ROIs, or provide results in coarsely-divided subregions of the hippocampus (head, body, and tail). Even though the body region can be divided into CA and DG subfields in the anatomical images, this segmentation is susceptible to confounding effects arising from signal variations caused by non-neuronal sources. Furthermore, all of these studies are limited by the spatial resolution of BOLD fMRI data (3 mm^3), whereas ≤2 mm^3 is commonly regarded as the appropriate resolution for detailed functional studies of the hippocampus[60]. In addition, transient brain and body states may influence fMRI measures at the time of imaging. Such transient states include multi-domain psychological (attention and sensory processing of irrelevant stimuli) and physiological states (arousal, sleep deprivation, or substances with pharmacologic central nervous system activity). Particularly, these studies were performed in a relatively small cohort regarding the unrelated samples (i.e. patients with diagnosis by mistake) that may have influenced the statistical power or sensitivity resulting in the identification of additional abnormal areas.

Task-Based Functional MRI

Recent task-based fMRI data from aMCI patients are also beginning to uncover relationships between abnormalities of functional activity in the hippocampus and functionally-connected cortical and subcortical regions. These data will contribute to our understanding of fundamental memory processes in the human brain and how they are perturbed in memory disorders.

Using a task involving the repetitive presentation of faces, Johnson and colleagues have shown that aMCI patients do not display the same slope of hippocampal hypoactivation with face repetition as that seen in older controls[61]. Using a face-name associative paradigm, Petrella and colleagues have found no differences in hippocampal activation during encoding, but reported left hippocampal hypoactivation during the retrieval condition (forced-choice recognition) in aMCI patients compared to controls. Furthermore, hippocampal hypoactivation is correlated with the clinical severity of memory loss in aMCI patients[62]. Using an item-based old/new recognition retrieval task, Johnson and colleagues have demonstrated right hippocampal hypoactivation in aMCI patients compared to controls[7]. In contrast, several studies have shown greater hippocampal activation in aMCI patients relative to controls. Using a visual encoding task, Dickerson and colleagues have shown that both hyperactivation in relatively more impaired aMCI patients and greater activation within the hippocampal formation are correlated with better memory performance[63]. In a separate study using the associative face-name encoding task, Dickerson and colleagues found hippocampal hyperactivation in very mild aMCI relative to controls[64]. The reason may be that the aMCI patients in that study were very mildly impaired based on the Clinical Dementia Rating, MMSE, and neuropsychological data, as well as performance of the fMRI memory task similar to controls. By separating the aMCI spectrum into two subgroups, the milder end and the more impaired end, Celone and colleagues demonstrated hyperactivation in the bilateral hippocampus in very mild aMCI, but hypoactivation in more impaired aMCI in an associative face-name encoding paradigm[65]. Using an item-based task with words, the first event-related subsequent memory study indicated that aMCI patients have activation in the rostral left hippocampus to a greater degree than controls[66]. These aMCI participants were at the more impaired end of the spectrum based on MMSE scores, but neuropsychological data indicated milder impairment compared to controls. In addition, the aMCI participants performed similarly to control participants in the fMRI memory task. Additional studies using event-related fMRI tasks[67] will be useful in determining whether increased activation of the hippocampus in aMCI is specifically associated with successful memory, as opposed to a general effect that is present regardless of success, possibly indicating increased effort. Using a visual scene-encoding task, Miller and colleagues also reported that greater hippocampal activation predicts a greater degree and rate of subsequent cognitive decline after controlling for baseline degree of impairment, age, sex, education, hippocampal volume, and APOE status[68]. Yassa and colleagues used a continuous recognition task that taxes the pattern-separation ability between similar studied and unstudied lure test items, and found hyperactivation localized to the CA3/DG subfield in aMCI patients[69]. Using

the encoding and retrieval phases of a memory task, de Rover and colleagues have reported that the bilateral hippocampal activation in aMCI patients and controls relies upon load, with the former activating significantly more than controls at low loads and significantly less at higher loads[70]. Using an incidental emotional memory test and fMRI measures, Parra and colleagues have shown that the recognition pattern in hippocampal activation is similar in aMCI patients and controls, but the extent of activation is stronger in the former[71]. Recently, in a likelihood-estimation meta-analysis of 28 fMRI studies, Nellessen and colleagues indicated that aMCI patients show enhanced right hippocampal activation during memory encoding and reduced activation in the left hippocampus during retrieval tasks[72].

Taken together, the evidence suggests that the variability in fMRI data from aMCI patients probably relates to the complex relationships between the severity of clinical impairment and their performance in the memory task used as the fMRI paradigm[73, 74]. One explanation is that these studies do not require participants to perform below a particular cutoff on neuropsychological memory tests, and therefore, some patients perform relatively well on neuropsychological testing, despite clinical manifestations of impaired memory in daily life. In addition, there may be two phases of decreased and increased hippocampal activation in the progression of aMCI. The phase of increased hippocampal activation may reflect a compensatory response to the pathology of AD. It is also probable that hyperactivation in the hippocampus reflects cholinergic or other neurotransmitter upregulation in aMCI patients[75]. Further research is needed to clarify these relationships and provide a deeper understanding that will be pivotal to our interpretation of imaging data.

A number of other factors are also likely to contribute to the variability in hippocampal activation. Some of the differences between studies may be due to the use of memory tasks that require different abilities and psychological resources. Examples of such differences are those between paired-associate and item-based memory, encoding and retrieval, and visual and verbal material. Further differences could stem from imaging analysis techniques (e.g. ROI *versus* voxel-based whole-brain methods) and the dependent variables that decide the level of activation (e.g. extent and magnitude of activation and voxel-based measures that include both extent and magnitude), and differences in age, sex, education, and APOE genotype[63]. Future studies will be crucial to clarify the contributions of these and other confounding factors to the variability in fMRI measures, if such techniques are to be converted into biomarkers for clinical trials.

More recently, the hippocampal neuroplasticity in aMCI patients has attracted increased attention and has been extensively investigated in fMRI studies. Using an auditory-verbal fMRI task, Rosen and colleagues have shown increased verbal memory scores and increased left hippocampal activation in a cognitive-training aMCI group compared to a control group. These data suggest that the hippocampus in aMCI may retain sufficient neuroplasticity to benefit from cognitive training[76]. In a randomized, controlled, single-blind fMRI study, Hampstead and colleagues demonstrated that, prior to mnemonic strategy training, aMCI patients show attenuated hippocampal activity compared to controls during both encoding and retrieval. After training, aMCI patients show increased activity during both encoding and retrieval, while there are no significant differences between the aMCI and matched-exposure controls in the right hippocampus during retrieval. This suggests that mnemonic strategy training promotes hippocampal function in a partially restorative way[77].

Combination of Structural MRI, Diffusion Tensor MRI, and Functional MRI Approaches in the Hippocampus of aMCI Patients

Recently, the combination of multi-modal MRI approaches to examine the hippocampus of aMCI patients has begun to show efficiency in asessing the progression of disease in precisely separated aMCI converters and non-converters, and in establishing objective and quantitative biomarkers for the conversion of aMCI to AD[78, 79].

Combining structural MRI and DTI techniques, Muller and colleagues have reported decreased volume in the left hippocampus and significant increases in MD in the bilateral hippocampus in aMCI patients compared to controls. These deficits are associated with poor verbal memory performance, and the data further suggest that a combination of macro- and microstructural parameters can enhance the early detection of neurodegenerative processes[80]. Subsequently, this research group compared the diagnostic accuracy of structural MRI and DTI techniques and reported that the left and right hippocampus

have different predictive power in these techniques[38]. By combining structural MRI and fMRI approaches in a visual object encoding task, Hamalainen and colleagues showed that aMCI patients have more atrophy in anterior parts of the left hippocampus and greater activation of the caudal hippocampal formation than controls. This information suggests that increased activation of the caudal hippocampus is compensatory, due to the initial atrophy in the anterior hippocampus[81]. Combining cortical volume and thickness measures with cognitive tests to predict the conversion of aMCI to AD, Liu and colleagues found decreased hippocampal volumes in progressive aMCI patients compared with controls and stable aMCI patients. However, this combination does not improve the accuracy of the measurements[24]. Combining structural MRI and fMRI methods, de Rover and colleagues showed that the functional activation deficit in aMCI is accompanied by structural atrophy in the hippocampus, which suggests that the decrease in hippocampal activation may contribute to the decreased amount of GM[70]. Palesi and colleagues combined structural MRI and DTI methods and reported that aMCI patients have reduced volumes and increased MD relative to controls, and verbal memory in MCI is correlated with the FA of total WM in the hippocampi and hippocampus-precuneus/PCC tracts. Both DTI and hippocampal volume measurements can reveal early signs of AD in aMCI patients[82]. In a meta-analysis that compared DTI to hippocampal measurements, Clerx and colleagues revealed that the effective size of the hippocampal MD is better than that of hippocampal volume in distinguishing aMCI from controls, and MD values are more discriminatory than FA values[83]. Douaud and colleagues examined both volumetric and microstructural abnormalities and found that progressive aMCI patients have significantly smaller GM volume in the left CA region and significantly higher MD in the left hippocampus compared to stable aMCI patients[84]. These findings highlight the benefit of using information about microstructural damage and traditional GM volume to detect early, mild abnormalities in aMCI patients prior to clinical progression to AD[84]. Another recent study combined structural MRI and fMRI methods and demonstrated that aMCI patients show GM volume loss in the bilateral hippocampus and significant decreases in the amplitude of low-frequency fluctuation (ALFF) in the left hippocampus. The GM volume and ALFF are correlated, suggesting that the anatomical and functional deficits are linked[85].

Based on these studies, the combination of multi-modal MRI approaches in the hippocampus can improve the precise classification of aMCI patients and controls and promises early detection of neurodegenerative processes. These results, however, are not consistent due to the differences in sample size, different research centers, and the ambiguous clinical stages of disease progression. Furthermore, sequential associations have not been established between macrostructural (volume and cortical thickness), microstructural (fiber integrity), and functional changes in the hippocampus (functional activation and functional connectivity), and neuropsychological performance. Further research is needed to establish a predictive model by combining these parameters of multi-modal MRI as predictors.

Perspectives

Numerous neuroimaging studies have indicated differences between “converters”, “stable” and “improved” groups of patients when analyzed retrospectively. Unfortunately, few studies have specifically addressed the issue of integrating different MRI approaches for efficient and quantitative diagnostics. The development of accurate and sensitive tools for the early diagnosis and monitoring of disease progression requires the discovery of new biomarkers in the asymptomatic and prodromal stages of AD. A universal and in-depth understanding of the interactions between biomarkers can be achieved using statistics and by selecting the proper model. Combination of structural and functional neuroimaging biomarkers in the progression of aMCI, the conversion of aMCI to AD, and the early diagnosis of AD, could lead to the standardization of imaging protocols and quantitative metrics. Before combinations of multi-modal MRI approaches can be considered as biomarkers and translated into clinical trials, the issues described in the following section need to be resolved.

Establishing More Precise Hippocampal Sub-regions Based on Structure and Function

The hippocampus is not an anatomically uniform structure; rather, it can be divided into subregions that perform different functions. Some studies have reported that the

progression in different subregions may be sequential in aMCI patients[19, 45]. However, previous studies have only provided results in coarsely-divided subregions. Therefore, more precisely-defined hippocampal subregions are needed for future studies, and they will facilitate the discovery of new multi-modal MRI biomarkers for the conversion of aMCI to AD.

Elucidating the Effects of APOE Polymorphism on Hippocampus in aMCI Patients

It is well known that the APOE genotype is associated with structural and functional changes in the early stages of AD. APOE is encoded by a polymorphic gene localized on chromosome 19 and exists as three alleles designated ε2, ε3, and ε4. Although these alleles differ by only single amino-acid substitutions, these small changes have profound functional consequences at both the cellular and molecular levels. APOE ε3 is the normal isoform, while ε4 and ε2 can be dysfunctional[86]. Recently, our research group reported that ε4 and ε2 have opposing effects on brain morphology across the spectrum of cognitive aging[15]. Because of this, it is important to investigate the effects of APOE genotype on the hippocampus in the progression of aMCI to AD.

Clarifying the Timing of Decline or Progression of aMCI to AD or Dementia

Another issue is that the ability to detect change is based on the period of observation that is predicted for the decline or progression of aMCI to AD or dementia. An in-depth understanding of the role of biomarkers in the prediction of decline in aMCI will require both short (1 to 2 years) and long-term (many years or even decades) periods of observation. Additional cross-sectional and longitudinal studies are needed to clarify the dynamic hippocampal changes in structure and function for the conversion of aMCI to AD over time.

Defining the Sequence of Hippocampal Changes Based on Multi-Modal MRI Measures in aMCI Patients

In the coming years, when many of the above issues have been resolved, we believe that a combination of advanced multi-modal MRI measures will provide more sensitive measures of hippocampal changes than the measures on their own in the progression of aMCI to AD. Furthermore, we propose a sequential and progressive framework for the progression of aMCI to AD (Fig. 1). First, the impairment changes from fiber integrity to volume and then

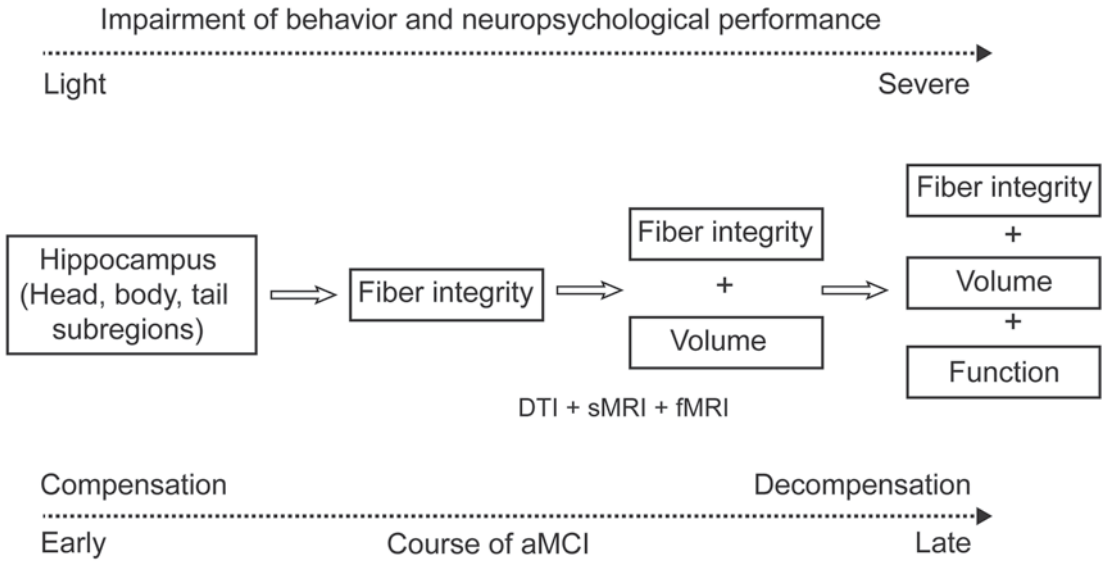

Fig. 1. Sequential and progressive structural and functional changes during the progression of aMCI to AD. The impairment changes from fiber integrity to volume and then from volume to function in hippocampal subregions. These changes accompany the progressive impairment of behavioral and neuropsychological performance in disease progression. fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; sMRI, structural magnetic resonance imaging.

from volume to function in the hippocampal subregions. In addition, these changes accompany the progressive impairment of behavioral and neuropsychological performance as the disease progresses. Early during the course of aMCI when the deficits of memory, fiber integrity, and volume are less prominent, there may be increased hippocampal connectivity, which could reflect an inefficient compensatory mechanism. Later during the course of aMCI, when the impairment of memory, fiber integrity, and volume is exacerbated, the hippocampal connectivity may be disrupted due to decompensation. Finally, longitudinal studies are pivotal to determine whether this hypothetical framework of the physiological, anatomical, functional, and behavioral progression of aMCI is supported by trajectories in individuals and groups of individuals.

In conclusion, we believe it is important in future studies to provide detailed demographic, clinical, neuropsychological, and behavioral memory performance data as well as multi-modal MRI data in the hippocampus and its subregions to help clarify the similarities or differences between samples of aMCI patients and the conversion of aMCI to AD over time.

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